REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-6 and 21-23 were examined. They are canceled in favor of new claims 21-40. Non-elected claims 7-20 were withdrawn from consideration by the Examiner. Applicants cancel the non-elected claims without prejudice to future prosecution of that subject matter. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. In particular, the enzymes are described on pages 9-20 of the specification, the pH requirements are described on pages 28-29 and Fig. 7 of the specification, and the divalent metal ion requirements are described on page 29 and Fig. 8 of the specification.

In satisfaction of their duties of good faith and candor, Applicants disclose their copending Application Nos. 10/492,819 and 10/507,421.

35 U.S.C. 101 –Utility

Claims 1-6 were rejected under Section 101 because they are allegedly reading on "non-statutory subject matter." Applicants traverse because adoption of the Examiner's suggestion to insert --isolated-- addresses the allegation as it might apply to the new claims.

Withdrawal of the Section 101 rejection is requested.

35 U.S.C. 112 – Definiteness

Claims 2 and 6 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Within the pH range from 5.0 to 7.5 shown in Applicants' specification, it is clear that the enzyme is least active from 6.2 to 6.6 depending on the buffer used. Neither the original claims nor the pending claims claim that enzyme activity is higher at pH 0-1 and 13-14 than at pH 6.2-6.6.

The Examiner's suggestion for amending the claims to recite "sequence identity" is adopted in the new claims.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1-3 and 6 were rejected under Section 112, first paragraph, because it was alleged that they contain "subject matter which was not disclosed in the specification in such a way as to reasonably convey to one of skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because the amendments address the Examiner's concerns.

The pending claims are directed to a genus of enzymes having "an amino acid sequence sharing at least 90% sequence identity with (i) SEQ ID NO: 2 from amino acid 189 to amino acid 500 or (ii) SEQ ID NO: 4 from amino acid 35 to amino acid 504." The structure is based on these two amino acid sequences. The human enzyme (SEQ ID NO: 2) and the mouse enzyme (SEQ ID NO: 4) share overall 88% sequence identity. This shows that amino acid sequences of at least 90% sequence identity would be reasonably expected to have the recited β1,3-N-acetyl-D-galactosamine transferase activity. Additionally, the amino acids indicated with an asterisk in Fig. 5 of the specification are conserved between the human and mouse enzymes for M1 (RNVIRSTWM), M2 (LLLKTDDDCY), and M3 (EDVSMGI) motifs that are conserved among β1-3Gal transferases. Moreover, the nonconservation of residues in the amino acid sequences shown in Figs. 5-6 of the specification demonstrated that substitutions, deletions, and insertions would be permitted in SEQ ID NOS: 2 and 4 without abolishing enzymatic activity. Therefore, it was incorrect to allege on pages 5-6 of the Action, "The structure of any polypeptide having the β1,3-N-acetyl-D-galactosamine transferase activity is

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte OLGA BANDMAN,
NEIL C. CORLEY, and PURVI SHAH

Appeal No. 2004-2319
Application No. 09/915,694

ON BRIEF

Before WILLIAM F. SMITH, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 3, 6, 7, 9 and 12. Claims 3 and 12 are representative of the subject matter on appeal, and read as follows:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 1; and
b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1.

12. An isolated polynucleotide selected from the group consisting of:
a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO: 2,
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2,
c) a polynucleotide having a sequence complementary to a polynucleotide of a),
d) a polynucleotide having a sequence complementary to a polynucleotide of b) and
e) an RNA equivalent of a)-d).

The examiner relies upon the following references:

Attwood et al. (Attwood), "Which craft is best in bioinformatics?," Computer and Chemistry, Vol. 25, pp. 329-339 (2001)

Ponting, "Issue in predicting protein function from sequence," Briefing in Bioinformatics, Vol. 2, No.1, pp. 19-29 (2001)

Claims 3, 6, 7, 9 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In addition, the claims stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. After careful review of the record and consideration of the issues before us, we reverse both rejections. We do, however, enter a new ground of rejection under 35 U.S.C. § 112, second paragraph over claim 12.

DISCUSSION

Written Description

Claims 3, 6, 7, 9 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventors, at the time the application was filed, had possession of the claimed invention.

According to the rejection:

> The claimed invention encompass[es] [sic] any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 (claim 3) and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2 (claim 12).

Examiner's Answer, page 3.

The rejection contends that the specification provides only a single representative species—an isolated polynucleotide consisting of SEQ ID NO: 2. The rejection asserts that "[t]here is no disclosure of any particular structure to function/activity relationship in the single disclosed species." Id. The rejection concludes "[g]iven this lack of additional representative species as encompassed by the claims, [appellants] have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize [appellants] were in possession of the claimed invention.

The written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus. See Utter v. Hiraga, 845 F.2d 993, 998, 6 USPQ2 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species the claim encompasses.").

The Court of Appeals for the Federal Circuit, our reviewing court, has addressed the issue of what constitutes adequate written description for a claim drawn to a nucleic acid. In Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1602 (Fed. Cir. 2002), the court adopted a portion of the Guidelines proffered by the United States Patent and Trademark Office (USPTO). The court stated that:

> The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics.

Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613 (citations omitted).

In Enzo-Biochem, the court refined the approach advanced by The Regents of The University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1998), adopting an example offered in the USPTO guidelines having facts that contrasted with those of Eli Lilly, wherein the written description requirement would be met. Adequate written description may be present for a genus of nucleic acids based on their hybridization properties, "if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." Enzo Biochem, 296 F.3d at 1327, 63 USPQ2d at 1615.

In the case before us, the complete structure of the polynucleotide of SEQ ID NO: 2 has been described, and the genus limited to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical

to the polynucleotide sequence of SEQ ID NO: 2. In addition, the complete structure of the polypeptide of SEQ ID NO: 1 has been described, and the genus limited to polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1. While the examiner asserts that the specification provides no disclosure of any particular structure to function/activity relationship in the single disclosed species, the examiner has not adequately explained and/or provided evidence to support that assertion. Thus, the rejection of claims 3, 6, 7, 9 and 12 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description, is reversed.

Enablement

Claims 3, 6, 7, 9 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

According to the rejection:

> The claimed invention encompass[es] [sic] any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 (claim 3) and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2 (claim 12).

Examiner's Answer, page 4.

The rejection contends that while the specification provides guidance for an isolated polynucleotide consisting of SEQ ID NO: 2, it "does not teach the

specific structural /catalytic amino acids and the structural motifs essential for protein activity/function which cannot be altered." Id. The rejection asserts further that

> The amount of experimentation to make the claimed polynucleotide is enormous and undue and entails selecting specific nucleotides to change (deletion insertion, substitution, or combinations thereof) in any polynucleotide to make a polynucleotide encoding a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 1 or selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in the nucleotide sequence of SEQ ID NO: 2 to make a polynucleotide that has a nucleotide sequence that is at least 95% identical to SEQ ID NO: 2 and determining by assays whether the encoded polypeptide has malate dehydrogenase activity.

Id. at 5.

Appellants argue that "[i]ndependent claim 3 recites not only that the 'variant' polynucleotides encode polypeptides that are at least 95% identical to SEQ ID NO: 1, but also have 'a naturally occurring amino acid sequence.'" Appeal Brief, page 10 (emphasis in original). Thus, appellants contend, "through the process of natural selection, nature will have determined the appropriate amino acid sequences," and given the information provided by SEQ ID NO: 1, the specification enables one skilled in the art to obtain a polynucleotide encoding a polypeptide comprising a naturally-occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1. We agree.

The examiner bears the initial burden of showing nonenablement. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' . . . That some

experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The examiner argues that "[t]he recitation of 'naturally occurring amino acid sequence' in the claims does not meet the enablement requirement since the specification must still provide guidance regarding the specific amino acid residues in the amino acid sequence of SEQ ID NO: 1 which cannot be changed and amino acid residues which can be changed but still retain malate dehydrogenase." Examiner's Answer, page 14. That argument is not agreed with because the examiner has not explained and/or provided evidence why a naturally occurring polynucleotide sequence that is at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2, or a naturally occurring polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 would not have malate dehydrogenase activity. As explained by appellants, "through the process of natural selection, nature will have determined the appropriate amino acid sequences." Thus, the rejection of claims 3, 6, 7, 9 and 12 under 35 U.S.C. § 112, first paragraph, for lack of enablement, is reversed.

NEW GROUND OF REJECTION

Under the provisions of 37 CFR § 41.50(b), we enter the following new ground of rejection: Claim 12 is rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The scope of the claim is indefinite because of its recitation of "a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2 . . . [and] an RNA equivalent [thereof]."

The normal meaning of "polynucleotide" is a polymer made up of nucleotides. Nucleotides are made up of a purine or pyrimidine base joined to a sugar residue (deoxyribose in DNA, ribose in RNA) and a phosphate group. Thus, according to its normal meaning, part (b) of claim 12 would encompass both DNA and RNA. Read in light of the rest of the claim and the specification, however, the scope of the claim becomes unclear.

First, SEQ ID NO:2 is a DNA sequence since it contains thymine (T) residues. The equivalent RNA sequence would have uracil (U) in place of thymidine. It is unclear, however, whether T and U would be considered to be "identical" residues in computing whether a given polynucleotide was "95% identical" to SEQ ID NO:2.

Second, if part (b) of claim 12 is intended to include both DNA and RNA, then part (e) of the claim is entirely superfluous. That is, there would be no need for a part (e) directed to "RNA equivalent[s]" unless parts (a) through (d) of claim 12 are intended to be limited to DNA, rather than encompassing both DNA and RNA.

These factors suggest that claim 12 uses the term "polynucleotide" as a synonym for DNA, rather than using it in its usual sense of encompassing both DNA and RNA. However, construing part (b) of the claim as limited to DNA presents its own problems. If part (b) of claim 12 were construed to encompass only "naturally occurring [DNA] sequence[s] at least 95% identical to the [DNA] sequence of SEQ ID NO:2", that part of the claim would very likely define a compound that does not exist.

The DNA shown in the specification's SEQ ID NO:2 is a cDNA sequence. See, working examples I, II and III (headed "THP1PLB01 cDNA Library Construction," "Isolation and Sequencing of cDNA Clones," and "Homology Searching of cDNA clones and Their Deduced Proteins," respectively).

cDNA sequences are not naturally occurring. They are laboratory-made DNA copies of naturally occurring messenger RNA (mRNA) sequences. The only naturally occurring DNA sequence that encodes the protein of SEQ ID NO:1 is a genomic sequence. That genomic sequence is then transcribed by the cell into an RNA equivalent that is processed and eventually translated into the polypeptide of SEQ ID NO:1. The processing steps required to generate an mRNA from a genomic DNA include removal of intervening sequences, or introns.

Virtually all human genes include introns. Thus, those skilled in the art would expect that the naturally occurring gene encoding the polypeptide of SEQ ID NO:1 would be interrupted by several introns. As a result, those skilled in the art would expect that, more likely than not, no naturally occurring DNA would be

95% identical to SEQ ID NO:2 because the parts of the naturally occurring gene that are identical to SEQ ID NO:2 would be interrupted by introns that are not part of the cDNA sequence of SEQ ID NO:2.

The naturally occurring gene that encodes the polypeptide of SEQ ID NO:1 would only fall within the scope of part (b) of claim 12 if it has introns that comprise 5% or less of its sequence. If the naturally occurring gene contains greater than 5% introns, it would appear that there is no naturally occurring DNA sequence that is 95% identical to SEQ ID NO:2. Thus, if part (b) of claim 12 is construed as being limited to DNA, it is overwhelmingly likely to be a nullity. It would add nothing to the scope of the claim.

On the other hand, if part (b) of claim 12 were construed to encompass both DNA and RNA, in addition to the ambiguities discussed above it would present issues of enablement that have not been discussed on the record. That is, if the claim encompasses both DNA and RNA, and if the corresponding genomic DNA does not contain an anomalously small amount of intron DNA, the only "naturally occurring" polynucleotides that would be 95% identical to SEQ ID NO:2 would be mRNAs (which are processed to excise introns).

Claim 12 is directed to an "isolated" polynucleotide, but the specification provides no guidance on how to isolate the particular mRNA corresponding to SEQ ID NO:2. Thus, if part (b) of claim 12 is construed to encompass both DNA and RNA, then for the reasons discussed above, the DNA aspect is probably a nullity and it is unclear whether the specification provides adequate guidance to

enable those skilled in the art to make and use the mRNA that represents the remainder of the invention defined by part (b).

Finally, even assuming that part (b) of claim 12 were construed to encompass naturally occurring mRNAs that are at least 95% identical to SEQ ID NO:2, and assuming that the specification provides an enabling disclosure for such mRNAs, the scope of the claims would still be unclear. The specification provides no guidance that would allow those skilled in the art to determine, with a reasonable degree of confidence, whether any of the sequences that are at least 95% identical to SEQ ID NO:2 occur naturally and, if so, which they would be. The only way to definitely fix the scope of the claims would be to compare SEQ ID NO:2 to all naturally occurring sequences, clearly an impossible task. Thus, even if we were to ignore the various ambiguities discussed above, the metes and bounds of the claim are unclear.

As the Federal Circuit recently noted,

> [t]he Supreme Court explained the reason underlying the indefiniteness doctrine 60 years ago in United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236, 55 USPQ 381, 385 (1942):
>
> > A zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims would discourage invention only a little less than unequivocal foreclosure of the field. Moreover, the claims must be reasonably clear-cut to enable courts to determine whether novelty and invention are genuine.

Exxon Research and Eng'g Co. v. United States, 265 F.3d 1371, 1376, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001). The court held that compliance with 35 U.S.C. § 112, second paragraph, is determined by "whether 'the claims at issue [are] sufficiently precise to permit a potential competitor to determine whether or

not he is infringing.'" Id. (bracketed text in original, quoting Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993)). That test is not met here.

For all these reasons, the scope of claim 12 is unclear. The test for definiteness is "whether one skilled in the art would understand the bounds of the claim when read in light of the specification." Miles Laboratories Inc. v. Shandon Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993). See also Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1342, 65 USPQ2d 1385, 1406 (Fed. Cir. 2003): "[A]mbiguity in claim scope is at the heart of the definiteness requirement of 35 U.S.C. § 112, ¶ 2." Since we cannot determine the scope of claim 12, we conclude that it is indefinite. Claim 12 is rejected under 35 U.S.C. § 112, second paragraph.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED, 37 CFR § 41.50(b)

William F. Smith Administrative Patent Judge	))))) BOARD OF PATENT
Eric Grimes Administrative Patent Judge	)) APPEALS AND)) INTERFERENCES
Lora M. Green Administrative Patent Judge	))

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completely undefined and the specification does not define the structural features necessary for members of the genus to be selected" (emphasis added) because Applicants have defined the structural features of their invention by reference to the human and mouse examples.

The written description requirement does not require a disclosure of the complete structure of every species within a chemical genus. See *Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all specifies the claim encompasses"). Multiple representatives of the genus are not required if common structural features are recited. See *Univ. of Calif. v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) ("A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus"). In similar fact situations as in this application, the Board of Patent Appeals and Interferences has reversed written description rejections with only a single, specific sequence disclosed in the specification. See *Ex parte Bandman* (Appeal No. 2003-1805 and 2004-2319), copies of which are attached. Here, two specific amino acid sequences are disclosed and their overall 88% sequence identity to each other support Applicants' teaching that amino acid sequences sharing at least 90% sequence identity with (i) SEQ ID NO: 2 from amino acid 189 to amino acid 500 or (ii) SEQ ID NO: 4 from amino acid 35 to amino acid 504 would be reasonably expected to have β1,3-N-acetyl-D-galactosamine transferase activity.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent

upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 1-3 and 6 were rejected under Section 112, first paragraph, because it was alleged that the specification "does not reasonably provide enablement for any isolated β1,3-N-acetyl-D-galactosamine transferase polypeptide having specific activity and biochemical characteristics and comprising an amino acid sequence having 30%-99% sequence identity to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4 or variants of said sequences in which one or several amino acids are substituted, deleted or inserted and having said specific activity and biochemical characteristics." Applicants traverse.

The human and mouse examples of the claimed invention, which have only 88% sequence identity, show that enzymatic activity would be retained after as many as 12% of their amino acid residues are substituted, deleted, or inserted. The high level of skill in the art, the disclosure of SEQ ID NOS: 2 and 4 with β1,3-N-acetyl-D-galactosamine transferase activity, the ability to make mutations in those sequences and to determine whether the mutated sequences are at least 90% identical to (i) SEQ ID NO: 2 from amino acid 189 to amino acid 500 or (ii) SEQ ID NO: 4 from amino acid 35 to amino acid 504, and the assaying of the mutated enzymes for activity does not amount to undue experimentation. Such work is routine in the art. Furthermore, the skilled person would know that comparisons such as shown in Figs. 5-6 and other requirements for enzymatic activity guide the making and using of enzymes within the scope of Applicants' claims. Either gene shuffling or in vitro evolution techniques using the disclosed sequences of β1,3-N-acetyl-D-galactosamine transferases would generate libraries of mutants that could be assayed for enzymatic activity.

The structural features of the invention recited in the claims and the teaching of conserved amino acid residues in Applicants' specification contradicts the allegation on page 9 of the Action that "the disclosure . . . provides no guidance with regard to the

making of variants and mutants" because, inter alia, nonconserved positions would be candidates for varying the amino acid sequence and conserved positions would be less likely to sustain mutation and still retain enzymatic activity. Moreover, gene shuffling and in vitro evolution techniques contradict the allegation on page 9 of the Action that "it is not routine in the art to screen for multiple substitutions or multiple modifications." The simple observation that the amino acid sequences of the human and mouse enzymes are only 88% identical is proof that multiple substitution or modification can be tolerated.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-6 directed to a protein were rejected under Section 102(b) as allegedly anticipated by Strausberg et al. (Proc. Natl. Acad. Sci. USA 99:16899-16903, 2002). Applicants traverse because the pending claims are directed to enzyme solution and processes of using them.

Strausberg et al. disclose a cDNA sequence that is predicted to encode a polypeptide. The putative enzyme was identified as an open reading frame. It is not clear from the brief description of their results whether a full-length cDNA clone was ever isolated or if the sequence was pieced together from shorter cDNAs ("Future Directions of the MGC Program. The goal of the MGC Program is to obtain a full-ORF cDNA sequence and clone for each human and mouse gene."). Thus, while the translation and isolation of a polypeptide are not disclosed in Strausberg et al., it not even clear whether one of skill in the art would have been able to produce an active enzyme from an available full-ORF cDNA clone. Certainly, in the absence of the isolated polypeptide, Straus-

berg et al. neither teach nor suggest the pH and divalent metal ion requirements for β1,3-N-acetyl-D-galactosamine transferase activity because it would have been impossible to have even predicted the enzyme's requirements without possession of the human enzyme.

Applicants claim an enzyme solution with a buffer having a pH and divalent metal ion constituents required for optimal β1,3-N-acetyl-D-galactosamine transferase activity and it use. In the absence of prior art polypeptide, one of skill in the art would not have been able to determine such requirements. These deficiencies in the disclosure of Strausberg et al. are sufficient to distinguish the claimed invention over the prior art so any other incorrect allegations about Strausberg et al. are not disputed here, but the opportunity to dispute them in the future is reserved.

Claims 1-3 and 6 directed to a protein were rejected under Section 102(b) as allegedly anticipated by Kawai et al. (Nature 409:685-690, 2001). Applicants traverse because the pending claims are directed to enzyme solutions and processes of using them.

Kawai et al. also disclose a cDNA sequence that is predicted to encode a polypeptide. The putative enzyme was identified as an open reading frame. But again the translation and isolation of a polypeptide are not disclosed by Kawai et al. In the absence of the isolated polypeptide, Kawai et al. can neither teach nor suggest the pH and divalent metal ion requirements for β1,3-N-acetyl-D-galactosamine transferase activity because it would have been impossible to have even predicted the enzyme's requirements without possession of the human enzyme.

Applicants claim an enzyme solution with a buffer having a pH and divalent metal ion constituents required for optimal β1,3-N-acetyl-D-galactosamine transferase activity and its use. In the absence of prior art polypeptide, one of skill in the art would not have been able to determine such requirements. These deficiencies in the disclosure of Kawai et al. are sufficient to distinguish the claimed invention over the prior art so any other incorrect allegations about Kawai et al. are not disputed here, but the opportunity to dispute them in the future is reserved.

Conclusion

Having fully responded to all of the pending objections and rejections contained in this Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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Paper No. 36

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte OLGA BANDMAN, JENNIFER L. HILLMAN, PREETI LAL, KARL J. GUEGLER, GINA GORGONE, NEIL C. CORLEY, CHANDRA PATTERSON, and MARIAH R. BAUGHN

Appeal No. 2003-1805
Application No. 09/079,892

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and GRIMES, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 25 through 28 and 33 through 37. Claims 6 through 12 are pending and have been allowed. Claims 29 through 32 are also pending but have been withdrawn from consideration by the examiner. Claims 25 and 33 are representative of the subject matter on appeal. Since claim 25 refers to allowed claim 7, we reproduce claims 7, 25, and 33 as follows:

7. An isolated and purified polynucleotide comprising a polynucleotide sequence as shown in SEQ ID NO:4, wherein said polynucleotide of SEQ ID NO:4 encodes a polypeptide having glutamine fructose-6-phosphate amidotransferase activity.

25. A method for detecting a target polynucleotide in a sample, wherein said target polynucleotide comprises the polynucleotide of claim 7, the method comprising:

a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

33. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:4,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:4,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

The examiner relies upon the following references:

Nishi et al. (Nishi '713)	5,876,713	Mar. 2, 1999
Eur. Pat. App. (Nishi EPA)	EP 824,149 A2	Feb. 18, 1998

Claims 33 through 37 stand rejected under 35 U.S.C. § 112, first paragraph (written description). Claims 25 through 28 and 37 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies upon Nishi '713 and Nishi EPA in the alternative. We reverse the written description rejection and affirm the obviousness rejection.

Background

The present invention involves human carbohydrate metabolism enzymes referred to by appellants as "CARM." Specification, page 5. As seen from claims 7, 25, and 33 reproduced above, the claims under review in this appeal involve the polynucleotide sequence as shown in SEQ ID NO:4 which is said to code for CARM-1. Id., page 19, lines 14 through 20. As explained:

> CARM-1 has chemical and structural similarity with human glutamine: fructose-6-phosphate amidotransferase (GI 183082). In particular, CARM-1 and human glutamine: fructose-6-phosphate amidotransferase share 78% identity. A fragment of SEQ ID NO:4 from about nucleotide 243 to about nucleotide 260 is useful, for example, as a hybridization probe. Northern analysis shows the expression of this sequence in various libraries, at least 51% of which are immortalized or cancerous and at least 46% of which involve immune response. Of particular note is the expression of CARM-1 in gastrointestinal, male and female reproductive, and nervous tissues.

Id., page 20, lines 4 through 11.

Discussion

1. Written description.

The examiner considers that claims 33 through 37 do not comply with the written description requirement of 35 U.S.C. § 112, first paragraph, since:

> The specification defines an 'allelic sequence' (see page 10) as an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered and that any given natural or recombinant gene may have none, one or many, allelic forms, and that common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, substitutions of nucleotides each of which may occur alone or in combination with the others one or more times in a given sequence. This definition does not provide any specific information about the structure of naturally occurring (alleles) variants of SEQ ID NO:4 (i.e. where are the regions within which mutations are likely to occur) nor discloses any function for naturally occurring variants. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:4 relates to the structure of any naturally

> occurring alleles. The general knowledge in the art concerning alleles does not provide any indication of how one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art structure of one does not provide guidance to the structure of others. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus (i.e. the sequence encoding SEQ ID NO:2) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Examiner's Answer, paragraph bridging pages 3 and 4.

The examiner also

> [F]ully acknowledges appellants' recitation of the structural limitations of the polynucleotides of claim 33 parts b) and d)-e). However, the polynucleotides as defined in claim 33 parts b) and d)-e) encompass a genus of polynucleotides that encompasses widely variant species, some having the same functions as the polypeptide of SEQ ID NO:1, some having unknown and distinctly different functions and some possibly having no function. While one of skill in the art, provided the polynucleotide sequence of SEQ ID NO:4, may be able to recognize variants of SEQ ID NO:4 with nucleotide sequence sharing 90% identity, one cannot recognize which of these variants occurs naturally and is thus encompassed by the genus of claim 33 part b). Therefore, the skilled artisan would not be able to recognize a member of the claimed genus of polynucleotides merely from its structural definition. This enormous genus will encompass a wide variety of polynucleotides with their own distinct properties. Because appellants have provided no functional limitation for the claimed polynucleotides, the single disclosed polynucleotide of SEQ NO:4 is not representative of the entire genus and one of skill in the art would not recognize that appellants were in possession of all polynucleotides comprising a naturally-occurring polynucleotide having at least 90% identity to SEQ ID NO:4 as encompassed by the claims.

Examiner's Answer, paragraph bridging pages 11 and 12.

The Federal Circuit discussed the application of the written description requirement to inventions in the field of biotechnology in University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), stating

that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials" Id. at 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

In reviewing this rejection, we note that the examiner has not rejected claim 8 under this section of the statute. Claim 8 reads:

8. An isolated and purified polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to the polynucleotide of SEQ ID NO:4, wherein said naturally occurring polynucleotide sequence encodes a polypeptide having glutamine-fructose-6-phosphate amidotransferase activity.

As seen, claim 8 differs from claim 33 b) which is the focus of the examiner's written description rejection in that it adds the limitation that the naturally occurring polynucleotide sequence encodes a polypeptide having glutamine-fructose-6-phosphate amidotransferase activity. Since the examiner has conceded that a claim having the scope of claim 8 complies with the written description requirement of 35 U.S.C. § 112, we do not find that the lack of a statement of function in claim 33 b) means that that portion of the claim lacks written descriptive support.

Claim 33 b) defines a genus of polynucleotides by way of two significant qualifiers. First, the polynucleotide of claim 33 b) must be "naturally occurring." Second, the polynucleotide of claim 33 b) must be "at least 90% identical to the polynucleotide sequence of SEQ ID NO:4." As explained in Lilly, a genus of polynucleotides can be described by a representative number of polynucleotides sharing common structural features which constitute a substantial portion of the genus. The examiner is correct in his analysis that claim 33 b) includes so-called nonfunctional alleles. However, those nonfunctional alleles must be "naturally occurring" and be at least "90% identical to the polynucleotide sequence of SEQ ID NO:4." In our view, these two limitations adequately describe the genus of polynucleotides encompassed by claim 33 b) without that claim further including a functional limitation.

We understand the examiner's concern that one may not recognize that a polynucleotide sequence having 90% identity with that of SEQ ID NO: 4 is "naturally occurring." However, that concern is more properly raised under a rejection under 35 U.S.C. § 112, second paragraph, rather than the written description requirement of the first paragraph.

The written description rejection is reversed.

2. Obviousness.

We initially note that appellants state that the claims are grouped together for the purposes of this rejection. Appeal Brief, page 5. Accordingly, we shall decide the issues raised in the Examiner's obviousness rejection as they pertain to claim 25. 37 CFR § 1.192(c)(7). We also note that the two Nishi references relied upon by the examiner appear to be the same. Thus, we shall consider the merits of the examiner's rejection as it is based upon Nishi '713.

Claim 25 is directed to a method for detecting a target polynucleotide said to comprise the polynucleotide of claim 7 in a sample. To this end, a sample is hybridized with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample. The probe will specifically hybridize to the target polynucleotide, if present, forming a hybridization complex. The presence or absence of the hybridization complex is an indication as to whether the sample contained the target polynucleotide.

The examiner has determined without dispute by appellants that Nishi '713 describes a polynucleotide encoding a carbohydrate metabolizing enzyme (glutamine:fructose-6-phosphate amidotransferase activity) that is 100% identical to the amino acid sequence set forth in SEQ ID NO:1 of this application. Examiner's Answer, page 6. The examiner has also determined, again without dispute by appellants, that Nishi '713 describes a polynucleotide sequence encoding that polypeptide that is 67.7% identical to the polynucleotide sequence set forth in SEQ ID NO:4 of this application. Id. The basis for the examiner's findings are the sequence comparison printouts

obtained as a result of an electronic search of sequence databases. As seen from the sequence search report dated December 14, 1999, U.S.-09-079-892-4.rng, pages 1-3 the polynucleotide sequence extending from nucleotide 99-2144 of SEQ ID NO:4 of this application is 100% identical to the coding sequence set forth in Nishi '713. See, e.g., Figs. 2A-2F and SEQ ID NO:5 of Nishi '713.

The examiner has concluded that it would have been obvious to a person of ordinary skill in the art to use any 20 contiguous nucleotides in the region of the polynucleotide sequence described in Nishi '713 as a probe in either a hybridization reaction or as part of a set of probes/primers in a PCR reaction to detect a target polynucleotide. Once again, appellants do not dispute this aspect of the examiner's position. Indeed, Nishi suggests as much, stating:

> The DNA encoding the protein or the partial peptide of the present invention can be cloned either by PCR amplification by using synthetic DNA primers having a partial nucleotide sequence of the DNA coding for the protein or by hybridization using the DNA inserted in a suitable vector and labeled DNA fragment or synthetic DNA coding for a part or full region of the protein or the partial peptide of the present invention. The hybridization can be carried out by the method described in Molecular Cloning, 2nd (J. Sambrook et al., Cold Spring Harbor Lab. Press, 1989). When a commercially available DNA library is used, the instructions given in the accompanying manual can be followed.

Nishi '713, column 15, lines 54 through 65.

Where the appellants and the examiner part company in regard to the obviousness rejection has to do with whether claim 25 on appeal is "directed only to detecting the target polynucleotides, comprising the polynucleotides recited in claim [] 7 . . ." (Appeal Brief, page 12) or whether claim 25 is inclusive of "detecting any target polynucleotide which hybridizes to probes generated from the sequence of

Nishi. . .." (Appeal Brief, page 11) (emphasis in each original). Appellants urge that claim 25 must be read such that the claimed method detects only the polynucleotides recited in claim 7. We disagree with appellants' claim construction.

First, appellants' position does not take into account that claim 25 explicitly reads upon a negative result, i.e., the probe comprising at least 20 contiguous nucleotides will not hybridize to any nucleotide sequence in the sample. This is seen in that claim 25 b) includes detecting the absence of a hybridization complex. Since appellants have not contravened the basic premise of the examiner's obviousness rejection, i.e., it would have been obvious to one of ordinary skill in the art to use a probe comprising at least 20 contiguous nucleotides based upon the polynucleotide sequence described in Nishi '713 in a hybridization method, the performance of such a method that results in a negative result reads directly upon claim 25. Thus, the examiner's rejection can be sustained on this basis.

Second, we do not read claim 25 in the manner in which appellants do. In our view, claim 25 is not limited "only to detecting the target polynucleotides comprising the polynucleotides recited in claim [] 7 . . .." Appeal Brief, page 12. Once a probe comprising at least 20 contiguous nucleotides is constructed based upon the polynucleotide sequence described in Nishi '713, the use of that probe in a hybridization method will result in the hybridization complex being formed if the probe hybridizes to any polynucleotide sequence in the sample under the hybridization conditions used. Thus, an appropriately constructed probe based upon the polynucleotide sequence described in Nishi '713 will hybridize to a polynucleotide sequence such as that of Nishi

'713, that of SEQ ID NO:4 of this application or any other polynucleotide sequence having sufficient complementarity given the hybridization conditions used.

The examiner's obviousness rejection is affirmed.

The decision of the examiner is affirmed-in-part.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

Sherman D. Winters
Administrative Patent Judge

William F. Smith
Administrative Patent Judge

Eric Grimes
Administrative Patent Judge

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